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OPERATION TREATY (PCT)

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(21) International Application Number: PCT/EP91/00619		(74) Common Representatives: COCKBAIN, Julian, R., M. et al.; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).	
(22) International Filing Date: 30 March 1991 (30.03.91)			
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(71) Applicant (for GB only): COCKBAIN, Julian, Roderick, Michaelson [GB/GB]; 27 Ladbroke Road, London W11 3PD (GB).			
(71) Applicant (for all designated States except US): NYCOMED AS [NO/NO]; Nycoveien 1-2, N-0401 Oslo 4 (NO).			
(72) Inventors; and (75) Inventors/Applicants (for US only) : KLAVENESS, Jo [NO/NO]; Skøyen Terrasse 15, N-0276 Oslo 2 (NO). EGE, Thorfinn [NO/NO]; Nycomed AS, Nycoveien 1-2, N-0401 Oslo 4 (NO). ROCKLAGE, Scott, M. [US/US]; 255 Cresci Road, Los Gatos, Sunnyvale, CA 95030 (US).		Published <i>With a revised version of the international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
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(54) Title: DIAGNOSTIC AGENTS			
(57) Abstract The use of superparamagnetic particles and of paramagnetic materials (such as lanthanide chelates) as contrast agents in magnetometric analysis, especially imaging, and in particular structural and functional, diagnosis or imaging is described.			

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INTERNATIONAL SEARCH REPORT

PCT/EP 91/00619

International Application No

I. CLASSIFICATION F SUBJECT MATTER (if several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁵ : A 61 K 49/00		
II. FIELDS SEARCHED Minimum Documentation Searched ? Classification System Classification Symbols IPC ⁵ A 61 K Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	IEEE Transactions on Magnetism, volume MAG-11, no. 2, March 1975, (New York, US) D. Cohen: "Measurements of the magnetic fields produced by the human heart, brain and lungs", pages 694-700, see page 694, abstract	1,4-7,27
Y	cited in the application --	1-8,27
X	IEEE Transactions on Magnetism, volume MAG-16, no.5, September 1980 (New York, US) D.E. Farrell et al.: "Magnetic measurement of human iron stores", pages 818-823, see page 818, abstract; page 819, paragraph 7 - page 820, paragraph 1	1,4-7,27
Y	cited in the application --	1-8,27
X	WO, A, 85/02772 (SCHRODER) 4 July 1985 see page 2, line 21 - page 3, line 1; page 5, line 35 - page 6, line 32	1,4-7,27
Y	cited in the application --	1-8,27
* Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 8th July 1991 International Searching Authority EUROPEAN PATENT OFFICE		Date of Mailing of this International Search Report 13. 11. 91 Signature of Authorized Officer  Natalie Weinberg

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ¹⁾ with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	WO, A, 88/00060 (ADVANCED MAGNETICS INC.) 14 January 1988, see page 10, line 29 - page 17, line 9 cited in the application	1,4-7,27
Y	-- WO, A, 86/06605 (THE GENERAL HOSPITAL CORP.) 20 November 1986, see page 1, line 13 - page 3, line 3; page 9, lines 22-31 cited in the application	1-8,27
Y	-- Chemical Abstracts, volume 104, no. 24, 16 June 1986 16 June 1986, (Columbus, Ohio, US) M.L. Cofield et al.: "Low-temperature magnetic susceptibilitz and zero-field splitting in some high-spin maganese (III) compounds", see page 704, abstract 217805s, & Inorg. Chim. Acta 1986, 112(1), 1-4	1-7,27
P,X	-- WO, A, 90/07322 (GORDON) 12 July 1990 see claims 17-19, 24	1-8,27

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers 9-16,28 because they relate to subject matter not required to be searched by this Authority, namely.

Please see attached sheet

2. ☒ Claim numbers 1-8, 27* because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically.

*Claims 27 searched incompletely
Please see attached sheet

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM

Claims 9-26, 28

Claims 9-17: "Methods for generating an image of a body comprising administration of a material to said body", and claims 18-26 and 28: "Processes for detecting magnetic susceptibility within a body comprising administering a material to said body" fall under the category of non-patentable subject matter given in Rule 39.1(iv) of the PCT

Claims 1-8, 27

The term "magnetometric" used in the claims is too vague and imprecise, and therefore not conforming to Article 6 of the PCT, to allow a complete, meaningful search to be carried out, the term has been interpreted from the description to mean "superconducting quantum interference device", and the search was performed on the basis that the term had this definition.

PCT

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International Bureau



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The use of superparamagnetic particles and of paramagnetic materials (such as lanthanide chelates) as contrast agents in magnetometric analysis, especially imaging, and in particular structural and functional, diagnosis or imaging is described.

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DIAGNOSTIC AGENTS

5 This invention relates to the use of paramagnetic and superparamagnetic substances as enhancing agents for diagnostic magnetometry, especially using a superconducting quantum interference device magnetometer (a SQUID) and preferably as imaging contrast agents in
10 magnetometric imaging, in particular SQUID imaging.

In 1963 James Zimmerman, a researcher at Ford Motor Company, observed that when a non-superconducting boundary is present in a superconducting loop a special effect is created. This effect is extremely sensitive
15 to magnetic flux and based on Zimmerman's work the very highly sensitive SQUID magnetometers have been developed and are now available commercially from companies such as Biomagnetic Technologies Inc of San Diego, California and Siemens AG of West Germany.

20 SQUID magnetometers generally comprise a superconducting pick up coil system and a detector system (the SQUID) which itself comprises one or two Josephson junctions inserted into a loop of superconducting wire. The magnetic flux within such
25 loops is quantized and changes in the magnetic field experienced by the pick up coils cause an immediate and measurable change in the current flowing through the detector. The SQUID magnetometers available include both single and multichannel devices, the latter being
30 capable of detecting magnetic fields at plurality of locations simultaneously.

SQUID magnetometers are capable of measuring magnetic fields as low as 10^{-14} Tesla, one ten billionth
the earth's magnetic field, and thus are able to detect
35 magnetic fields generated by biological activity such as for example the fields of the order of 10^{-13} T which are induced by the electrical activity of the brain. The

sources of nerve signals can thus be traced to within a few millimeters.

SQUIDS and their use in the study of biomagnetism are discussed for example by Wolsky et al. Scientific American, February 1989, pages 60-69, Philo et al. Rev. Sci. Instrum. 48:1529-1536 (1977), Cohen IEEE Trans. Mag. MAG-11(2):694-700 (1975), Farrell et al. Applied Physics Communications 1(1):1-7 (1981), Farrell et al. IEEE Trans. Mag. 16:818-823 (1980), and Brittenham et al. N. Eng. J. Med. 307(27):1671-1675 (1982). The SQUID may be designed to detect the magnetic field or, may be of the gradiometer type and which several designs exist.

Indeed the development of biomagnetic analysis has been closely linked to the development of SQUID detectors since conventional magnetometers, such as Bartington detectors or Hall-probe gaussmeters, are several orders of magnitude less sensitive to magnetic field changes.

In the study of biomagnetism, or more specifically, the in vivo measurement of magnetic susceptibility, the sensitivity of SQUIDS has been such that the researchers' concentration has primarily been on three areas - the detection of electrical activity within body tissues by detection of the accompanying magnetic field changes, the in vivo determination of iron concentrations in the liver in order to detect iron overload or iron deficiency there, and the detection of ferromagnetic particle contamination in the lungs.

In the first two cases, the magnetic fields detected by the SQUIDS arise from normal or stimulated nerve activity or from the normal presence of (paramagnetic) iron in the liver. In the third case, particle contamination is by magnetic particles, e.g. of magnetite, and their magnetic effect is first maximized by placing the subject in a magnetic field. The resultant magnetization is detectable by a SQUID for the

period of months over which it decays.

Due to the extreme sensitivity of the SQUID technology enabling the body's electrical activity to be monitored, there has been little emphasis on the use of SQUIDS for the generation of images, in particular two or three dimensional images, of the body's internal physical structure rather than electrical activity images.

For such localisation to be effective it must be possible to generate magnetic susceptibility differences between different body tissues, organs and ducts and rather than doing this by provoking electrical activity or by relying on natural aggregations of non-diamagnetic material we now propose the administration in diagnostic magnetometry, especially magnetometric imaging, of enhancing agents comprising paramagnetic or superparamagnetic substances. SQUIDS are sufficiently sensitive to detect the changes in local magnetic susceptibility where such agents distribute within the body so enabling contrast enhanced magnetometric signals or images to be generated, for example for use in diagnostics.

Thus viewed from one aspect the present invention provides the use of a physiologically tolerable paramagnetic or superparamagnetic material, and in particular paramagnetic lanthanide metal ion chelates and free or matrix borne superparamagnetic particles, for the manufacture of a diagnostic agent for use in magnetometric analysis, preferably by magnetometric imaging, of the human or non-human, preferably mammalian, animal body.

Viewed from a further aspect, the invention also provides a method of diagnosis of the human or non-human animal body which method comprises administering to said body a physiologically tolerable paramagnetic or superparamagnetic material and generating a magnetometric signal of at least a part of said body

into which said material distributes, preferably but not essentially using a SQUID based system, especially a multichannel SQUID.

5 Viewed from another aspect the invention also provides a method of generating a magnetometric image of the human or non-human animal body which method comprises administering to said body a physiologically tolerable paramagnetic or superparamagnetic material and generating a magnetometric image of at least a part of 10 said body into which said material distributes, in particular generating a two or three dimensional structural image and preferably but not essentially using a SQUID based imaging device, especially a multichannel SQUID imager.

15 Viewed from a still further aspect, the invention also provides a process for detecting variations in magnetic susceptibility within a human or non-human animal body which process comprises administering to said body a physiologically tolerable paramagnetic or 20 superparamagnetic material, and with a magnetometer continuously or repeatedly monitoring the magnetic susceptibility of at least a part of said body into which said material distributes, for example to generate magnetometric signals or preferably images of variations 25 or abnormalities in blood flow, or to monitor the location and aggregation of these materials within regions of the body, for example the arrival and accumulation of tissue- or organ- targeting substances at the targeted region, e.g. a tumour, the 30 reticuloendothelial system, etc. and optionally to generate a magnetometric image thereof.

Viewed from another aspect the invention also provides the use of a physiologically tolerable paramagnetic or superparamagnetic material, and in 35 particular paramagnetic lanthanide metal ion chelates and free or matrix borne superparamagnetic particles, for the manufacture of a diagnostic composition for use

in the process according to the invention.

The method and process of the invention may be performed using any magnetometric technique but are particularly suited to the use of SQUID based magnetometers. Thus the process of the invention for example may be performed using single channel SQUIDS but would preferably be performed using a multichannel SQUID system.

The paramagnetic or superparamagnetic substances used according to the invention and for convenience referred to herein as magnetometric diagnostic agents may, in view of the sensitivity of SQUID magnetometers, be any such material which is biotolerable in the dosages and with the administration form and route that is used. There is of course no necessity to pre-magnetize the subject following administration of the diagnostic agent before transferring the subject to the magnetometer location (generally a region of homogeneous magnetic field or a magnetically shielded room). However, the contrast agent may be pre-magnetised before administration and it may also be advantageous to pre-treat the magnetic substance to prevent conglomeration thus obtaining a maximum field for a given concentration of substance.

The process and method of the invention can be performed with or without the imposition of an external magnetic field (besides or in place of the earth's natural magnetic field that is). Imposed fields can be variant, e.g. pulsed, or invariant. Where the contrast agent used is superparamagnetic the method and particularly the process of the invention may advantageously be performed with no pre-magnetization and with no imposed magnetic field or with only a static imposed magnetic field. However where the contrast agent used is paramagnetic rather than superparamagnetic, the magnetometric investigation according to the invention will preferably be performed with the

subject exposed to an imposed pulsed or invariant magnetic field, at least in the region of interest. This field can be relatively localized in effect and can be as low as 10^{-4} T but in one convenient embodiment may be the primary field, generally of up to 10^1 T, generated by the primary coils of a magnetic resonance imager. Where the contrast agent is superparamagnetic an external field can be but need not be applied.

Particularly preferred diagnostic agents will include those which have relatively high magnetic susceptibilities, in particular superparamagnetic particles and substances containing high spin paramagnetic metal species, especially high spin transition metal and lanthanide ions, in particular ions of Mn, Fe, Dy, Gd, Eu, Tb, Tm, Yb, Er and Ho, most particularly Dy(III). A wide variety of such materials have been proposed for use as contrast agents in magnetic resonance imaging (MRI), and MRI contrast agents will in general also be suitable for use as magnetometric diagnostic (MD) agents, including magnetometric imaging (MI), contrast agents.

Thus particular mention may be made of the superparamagnetic contrast agents already proposed for use as MRI contrast agents by for example Jacobsen et al. in US-A-4863716, by Klaveness et al. in WO-A-89/11873, by Schröder et al. in WO-A-85/02772, by Groman in WO-A-88/00060, by Schering in EP-A-186616, by Widder et al. in AJR 148:399-404 (1987), by Hemmingsson et al. in Acta Radiologica 28:703-705 (1987), by Hahn et al. in Society of Magnetic Resonance in Medicine, 7th Annual Meeting, 1988, Book of Abstracts, page 738, by Saini et al. in Radiology 162:211-216 (1987), by Clement et al. in CMR89. MR20 (1989), etc.

Superparamagnetic particles free and carrier-bound are widely available and their preparation is described in a large variety of references, e.g. WO-A-83/03920 (Ugelstad), WO-A-89/03675 (Schröder), WO-A-83/03426

(Schröder), WO-A-88/06632 (Josephson), US-A-4675173, DE-A-3508000, US-A-4827945; US-A-4951675 and WO-A-88/00060.

5 The literature thus contains many suggestions for the formulation of superparamagnetic particles and in particular suggests that the particles can be administered either free (i.e. uncoated and not bound to any other substance) or coated (e.g. dextran coated - see for example US-A-4452773) or carried by or embedded in a matrix particle (e.g. a polysaccharide -see for example WO-A-83/03920 and WO-A-85/02772) or bound to an organ or tissue targetting species, e.g. a biomolecule such as an antibody or a hormone (see for example WO-A-88/00060 and WO-A-88/06632).

15 Due to the sensitivity of SQUIDS, which should be able to detect very small numbers of or even single superparamagnetic crystal loaded matrix particles, tumour imaging or detection using antibody-coupled superparamagnetic particles may be of significant practical interest.

20 For such tumour imaging or detection, one may conveniently use superparamagnetic crystal loaded matrix particles where the matrix is coupled to an antibody, or coated, e.g. silanized, superparamagnetic crystals where the coating is coupled to an antibody, or even paramagnetic polychelates coupled to an antibody, preferably ones in which the chelated paramagnetic ions are high spin lanthanides such as Dy(III), Ho(III) and Er(III). Paramagnetic polychelates have received much attention recently as potential X-ray and MRI contrast agents and are discussed for example in WO-A-90/12050.

25 Parenterally administrable particulate MD agents are also of particular interest in the imaging of the liver and spleen due to the action of the reticuloendothelial system in removing such particles from the blood stream. However MD agents and especially particulate agents may also be used to advantage in the

magnetometric diagnosis or imaging of body ducts and cavities having external voidance ducts, e.g. the gastrointestinal tract, the bladder and the uterus, where the MD agent can be administered orally, rectally or through a catheter into the body cavity of interest.

Many different ways of achieving tissue and organ specificity for soluble and particulate diagnostic agents are already known.

Thus by attachment to fatty acids and other substances with a specific hydrophilic/hydrophobic ratio the agent will after intravenous injection efficiently accumulate in the hepatocytes. Hepatocytes also have specific lectins present on their surface. The latter causes specific oligosaccharides and glycoproteins to accumulate in the hepatocyte compartment of the liver. The Kupffer cells as well as the endothelial cells of the liver also possess unique lectins on their surface, causing other types of glycoproteins to accumulate in these compartments. The endothelial cells of the liver have receptors for specific molecules such as hyaluronic acid, enabling other types of targeting vehicles also to be used for this compartment.

It is possible to bind the MD agent to monoclonal antibodies specific for almost any macromolecular structure. Different organs have cells containing organ-specific structures on their surface. Using monoclonal antibodies reacting with organ-specific structure, it is thus possible to produce organ-specific vehicles.

Furthermore, hormones, growth factors and lymphokines often have organ-specific receptors. Consequently, "natural" human proteins of this type may also be used as targeting vehicles.

These types of targeting vehicles will cause accumulation in normal organs, and if these are deformed and non-homogeneous due to disease, MD agents attached to such vehicles will provide important diagnostic

information. However, for direct disease visualization, targeting vehicles with affinity for disease-specific structures should be employed.

Thus tumour cells possess unique surface markers, and monoclonal antibodies reacting with a number of such structures have been developed. Tumor-specific monoclonal antibodies coupled to MD agents can thus be used to obtain disease information, e.g. by visualization.

Thrombi contain a number of specific structures, for instance fibrin. Consequently, MD agents coupled to fibrin-specific antibodies will after intravenous injection accumulate in the clots, and can be used for diagnosis of the thrombi.

In the same way as Mabs with affinity for clots can be developed, the naturally occurring protein tPA has affinity for fibrin. tPA coupled MD agents would thus accumulate in thrombi and be useful for their detection.

Upon cell necrosis, intracellular structures like myocine and histones are exposed to macromolecules normally confined to the extracellular space. Coupled to MD agents Mabs against both the above structures may thus be used to visualise infarcts/necrosis.

Where superparamagnetic particle containing contrast media are administered parenterally, and especially intravascularly, the biodegradation and ultimate excretion of the particle metabolites may be enhanced by formulating the particles together with a chelating agent as described in WO-A-89/11873.

The superparamagnetic particles themselves may be of any material which, although preferably non-radioactive (unless the particles are also intended to be detected by their radioactive decay emissions), exhibits superparamagnetism in domain and sub-domain sized crystals. Conveniently the particles will be of a magnetic metal or alloy, e.g. of pure iron, but more preferably they will be of a magnetic iron oxide, e.g.

magnetite or a ferrite such as cobalt, nickel or manganese ferrites.

For use as MD agents or tracers particular mention may also be made of the paramagnetic metal complexes, especially chelate complexes, which have been proposed for use as MRI or X-ray contrast agents.

For paramagnetic metals to be administered at effective but non-toxic doses, they will generally be administered in the form of ionic or more preferably, especially at higher dosage levels, non-ionic complexes, especially chelate complexes optionally bound to larger carrier or targeting molecules which may be selected to achieve a particular biodistribution of the MD agent - e.g. to produce a blood pooling or tissue- or organ-targeting agent - or to reduce the osmolality of the MD medium by increasing the number of paramagnetic centres per MD agent molecule (or molecular ion).

A wide range of suitable chelants, polychelants, and macromolecule-bound chelants for paramagnetic metal ions has been proposed in the patent literature over the last decade and in this respect particular regard may be had to US-A-4687659 (Quay), US-A-4647447 (Gries), US-A-4639365 (Sherry), EP-A-186947 (Nycomed), EP-A-299795 (Nycomed), WO-A-89/06979 (Nycomed), EP-A-331616 (Schering), EP-A-292689 (Squibb), EP-A-232751 (Squibb), EP-A-230893 (Bracco), EP-A-255471 (Schering), EP-A-277088 (Schering), EP-A-287465 (Guerbet), WO-A-85/05554 (Amersham) and the documents referred to therein, the disclosures of all of which are incorporated herein by reference.

Particularly suitable chelants for the formation of paramagnetic metal chelate MD agents for use in the method and process of the present invention include the following:

N,N,N',N'',N'''-diethylenetriaminepentaacetic acid (DTPA), 6-carboxymethyl-3,9-bis(methylcarbamoyl-methyl)-3,6,9-triazaundecanedioic acid (DTPA-BMA),

6-carboxymethyl-3,9-bis(morpholinocarbonylmethyl)-
-3,6,9-triazaundecanedioic acid (DTPA-BMO),
1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic
acid (DOTA),
5 1,4,7,10-tetraazacyclododecane-N,N',N''-triacetic acid
(DO3A),
1-(2-hydroxypropyl)-1,4,7,10-tetraaza-N,N',N''-triacetic
acid (HP-DO3A),
1-oxa-4,7,10- triazacyclododecane-N,N',N''-triacetic
10 acid (DOXA), polylysine-bound DTPA and DTPA derivatives
and DO3A and DO3A derivatives (e.g. DTPA-polylysine and
DO3A-polylysine), dextran-bound DTPA and DTPA
derivatives (DTPA-dextran) especially soluble materials
which, having a total molecular weight ≥ 40 KD,
15 preferably in the range 60-100 KD, are effective as
blood pooling agents.

Particularly suitable paramagnetic metal ions for
chelation by such chelates are ions of metals of atomic
numbers 21 to 29, 42, 44 and 57 to 71, especially 57 to
20 71, more especially Cr, V, Mn, Fe, Co, Pr, Nd, Eu, Gd,
Tb, Dy, Ho, Er, Tm, Yb and Lu, in particular Cr(III),
Cr(II), V(II), Mn(III), Mn(II), Fe(III), Fe(II) and
Co(II), more especially Gd(III), Tb(III), Dy(III),
Ho(III), Er(III), Tm(III) and Yb(III), more particularly
25 Dy(III), Ho(III) and Er(III).

In order to perform the methods of the invention
with as high as possible a safety factor (the ratio
between the dose of the MD agent and its LD_{50}), it is
particularly preferred to use non-ionic or low
30 osmolality chelates, i.e. chelates which carry no
overall ionic charge, such as DyDTPA-BMA for example, or
in which the complex has an overall ionic charge to
paramagnetic metal centre ratio of 1.5 or less.

Furthermore, where it is desired that the MD agent
35 should remain wholly or essentially within a body duct,
e.g. the blood vessels, during passage through the body
region of interest, the MD agent will preferably be

particulate, hydrophilic or blood-pooling.

Examples of suitable blood-pooling agents include the inert soluble macromolecule-bound chelates of the type described by Nycomed in EP-A-186947 and
5 WO-A-89/06979. Binding the chelant to a macromolecule, e.g. a polysaccharide such as dextran or derivatives thereof, to produce a soluble macromolecular chelant having a molecular weight above the kidney threshold, about 40 KD, ensures relatively long term retention of
10 the contrast agent within the cardiovascular system.

Examples of suitable hydrophilic MD agents include linear, branched or macrocyclic polyaminopolycarboxylic acid chelates of paramagnetic metal ions, and also especially include chelates of chelants in which one or
15 more carboxylic acid groupings are replaced by other groups such as amides, esters or hydroxamates, as well as such chelants in which the chelant backbone is substituted by hydrophilic groupings such as for example hydroxyalkyl or alkoxyalkyl groups. Chelants of these
20 types are disclosed for example in US-A-4687658 (Quay), US-A-4687659 (Quay), EP-A-299795 (Nycomed) and EP-A-130934 (Schering).

Particular mention however must be made of the Gd(III), Dy(III), Ho(III) and Er(III) chelates of DTPA-
25 BMA, DTPA-BMO, HP-DO3A and DO3A.

Physiologically tolerable paramagnetic porphyrin complexes, especially complexes of Mn(III) and less preferably of Gd(III) or Dy(III), may also be used according to the invention with particular effect, e.g.
30 in tumour localization. Such porphyrin complexes are described, for example, by Lyon et al. in Magnetic Resonance in Medicine 4 : 24-33 (1987), by Chen et al. in FEBS 1274 168 : 70 (1984) and in US-A-4783529 (Lavelle). Particular mention may be made of
35 hematoporphyrin, preferably complexed to Mn(III) but which may also be used with cobalt-58, Zinc-65 and palladium-109 as described by Bohdiewicz et al. Invest.

Radiology 25 : 765-770 (1990). Porphyrins such as tetrakis(4-sulfonatophenyl)porphyrin (TPPS) and tetrakis(N-methyl-4-pyridyl)porphyrin (TMPyP) are already known as MRI contrast agents and are described in the literature (see for example Helpert et al. in Magnetic Resonance in Medicine 5 : 302-305 (1987), Patronas et al. in Cancer Treatment Reports 70 No. 3 p391 (1986), Fiel et al. in Magnetic Resonance Imaging 5 : 149-156 (1987) and Chen et al. supra). To accommodate a larger metal ion (e.g. Gd (III)) a so-called "expanded porphyrin" (texaphyrin) as described in WO-A-90/10633 (University of Texas), J. Am. Chem. Soc. 110 : 5586-5588 (1988) (Sessler et al.) and Inorganic Chemistry 28 : 3390-3393 (1989) (Sessler et al.) may be used according to the invention.

Moreover, magnifier paramagnetic complexes, optionally bound to targeting biomolecules or macromolecules such as those described in WO-A-90/12050 may also be used to particular effect.

The dosages of the MD agent used according to the method of the present invention will vary according to the precise nature of the MD agent used, of the magnetometer being used and of the tissue or organ of interest. Preferably however the dosage should be kept as low as possible while still achieving a detectable variation in magnetic susceptibility.

In general, the MD agents used according to the invention should be administered in a quantity sufficient to produce a concentration, expressed in terms of susceptibility of at least 10^{-9} emu/g, preferably at least 5×10^{-9} emu/g, especially at least 10^{-8} emu/g.

Thus viewed from a further aspect the invention provides a magnetic susceptibility MD medium in aqueous form containing a physiologically tolerable paramagnetic or superparamagnetic substance together with at least one pharmaceutical carrier or excipient, the magnetic

susceptibility of said medium (at STP) being in the range 10^{-12} to 10^{-6} , preferably 10^{-11} to 2×10^{-7} , especially preferably 10^{-10} to 5×10^{-8} , in particular 10^{-9} to 10^{-8} , emu/g.

5 Alternatively expressed, for most paramagnetic and superparamagnetic materials the novel MD media will conveniently contain the magnetic metal at a concentration of at least 10^{-14} M, generally at least 10^{-10} M, preferably at least 10^{-8} M, in particular at least
10 0.05 mM, especially at least 0.2 mM, more preferably at least 0.3 mM, most preferably at least 1.0 mM, e.g. 0.0002 to 2 M, more especially 0.0003 to 1.5 M.

The MD media of the invention may contain particularly low concentrations of the contrast agent
15 where it is a highly specifically targeted material. Thus for an agent specific for small tumours minimum dosages of the order of 10^{-14} M/Kg may be adequate, for liver specific agents minimum dosages may be of the order of 10^{-11} M/Kg and for agents which distribute
20 broadly within the body minimum dosages of 10^{-10} M/kg may be appropriate. These will generally be administered in volumes of 0.1 ml to 1000 ml. The upper limit for MD agent dosages will be generally comparable to that for MRI contrast agents and may be dictated by toxicity
25 constraints.

For most MD agents the appropriate dosage will generally lie in the range 0.02 μ mol to 3 mmol paramagnetic metal/kg bodyweight, especially 1 μ mol to 1.5 mmol/kg, particularly 0.01 to 0.5, and more
30 especially 0.1 to 0.4 mmol/kg.

Where less sensitive non-SQUID magnetometers are used according to the invention, the MD agent concentrations required will of course be higher than are needed using SQUID magnetometers.

35 It is well within the skill of the average practitioner in this field to determine the optimum dosage for any particular MD agent by simple experiment,

either in vivo or in vitro.

Where the MD agent is ionic, such as is the case with DyDTPA, it will conveniently be used in the form of a salt with a physiologically acceptable counterion, for example an ammonium, substituted ammonium, alkali metal or alkaline earth metal cation or an anion deriving from an inorganic or organic acid. In this regard, meglumine salts are particularly preferred.

MD agents may be formulated with conventional pharmaceutical or veterinary aids, for example, stabilizers, antioxidants, osmolality adjusting agents, buffers, pH adjusting agents, etc., and may be in a form suitable for enteral or parenteral administration, e.g. oral, rectal, intravascular etc. Particularly preferably the MD agents will be in forms suitable for ingestion, injection or infusion directly or after dispersion in or dilution with a physiologically acceptable carrier medium, e.g. water for injections. Thus the contrast agents may be formulated in conventional administration forms such as powders, solutions, suspensions, dispersions etc., however solutions, suspensions and dispersions in physiologically acceptable carrier media will generally be preferred.

The MD agents may therefore be formulated for administration using physiologically acceptable carriers or excipients in a manner fully within the skill of the art. For example, the MD agents optionally with the addition of pharmaceutically acceptable excipients, may be suspended or dissolved in an aqueous medium, with the resulting solution or suspension then being sterilized. Suitable additives include, for example, physiologically biocompatible buffers—chelating agents (as for example DTPA or DTPA-bisamide (e.g. 6-carboxymethyl-3,9-bis(methylcarbamoyl methyl)-3,6,9-triazaundecanedioic acid)) or calcium chelate complexes (as for example salt forms of the calcium DTPA complex or the calcium DTPA-

bisamide complex, such as NaCaDTPA-bisamide) or, optionally, additions (e.g. 1 to 50 mole percent) of calcium or sodium salts (for example, calcium chloride, calcium ascorbate, calcium gluconate or calcium lactate and the like).

Parenterally administerable forms, e.g., intravenous solutions, should of course be sterile and free from physiologically unacceptable agents, and should have low osmolality to minimize irritation or other adverse effects upon administration and thus the MD medium should preferably be isotonic or slightly hypertonic. Suitable vehicles include aqueous vehicles customarily used for administering parenteral solutions such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection and other solutions such as are described in Remington's Pharmaceutical Sciences, 15th ed., Easton: Mack Publishing Co., pp. 1405-1412 and 1461-1487 (1975) and The National Formulary XIV, 14th ed. Washington: American Pharmaceutical Association (1975). The solutions can contain preservatives, antimicrobial agents, buffers and antioxidants conventionally used for parenteral solutions, excipients and other additives which are compatible with the MD agents and which will not interfere with the manufacture, storage or use of the products.

It will be realized of course that since the MRI contrast media can be used as MD media it will be particularly convenient to investigate the subject using MRI to supplement or confirm diagnostic information derived from the magnetometer investigations. Moreover, images from MRI on other conventional imaging modalities may be used to provide a "native" image onto which the magnetometric information or image may be superimposed - this is of particular value where the biodistribution of the magnetometric contrast agent is very limited.

The invention will now be illustrated further with reference to the following non-limiting Examples.

Example 1

- 5 Intravenous superparamagnetic MD agent for liver, spleen and perfusion studies (Dextran-coated superparamagnetic particles)

10 Dextran-coated superparamagnetic particles are prepared from FeCl_2 , FeCl_3 and dextran according to Example 7.1 in WO-A-88/00060 (Advanced Magnetics).
Average particle size: 140 nm

- 15 An injectable dispersion is prepared which contains:
Dextran-coated superparamagnetic particles 20 mg
Saline solution (0.9% sodium chloride) ad 10 ml.

20 The superparamagnetic particles are dispersed in saline solution and filled into 10 ml vials under aseptic conditions. The suspension is sonicated before administration to ensure complete dispersion of the particles.

Example 2

- 25 Intravenous superparamagnetic MD agent for tumour studies (Monoclonal antibody-coated magnetite particles)

30 Monoclonal antibody-coated superparamagnetic particles are prepared according to the method of S. Cerdan et al., Magnetic Resonance in Medicine 12:151-163 (1989).

35 The antibody is 33B31 (an antibody to IL-2 available from Immunotech), PP1 (an antibody to sarcoma available from Fodstad, Norwegian Radium Hospital, Oslo), or S4H9 (an antibody to the D2 fragment of fibrinogen available from Nycomed AS).

A dispersion of the particles is filled into 20 ml vials and freeze dried. Each vial contains 48 mg Fe.

5 The product is dispersed in 10 ml saline before administration.

Example 3

Intravenous paramagnetic MD agent for tumour studies
(Monoclonal antibody labelled with stable free radicals)

10

2,2,5,5-tetramethyl-3-aminopyrrolidone-1-oxide radical is coupled to monoclonal antibody according to the methods described in US-A-3453288.

15 The antibody is as in Example 2.

A solution of the labelled antibody is filled into 10 ml vials and freeze dried. Each vial contains 0.5 mmol nitroxide radicals.

20

The product is dissolved in 5 ml saline before use.

Example 4

25 Intravenous paramagnetic MD agent for perfusion studies
(Dextran 70-beta-alanine-DOTA-Dy)

Dextran 70-beta-alanine-DOTA-Dy is prepared according to Example 6 in EP-A-326226 (Nycomed).

30

An injectable solution is prepared which contains:

Dextran 70-beta-alanine-DOTA-Dy 2320 mg

Saline solution ad 10 ml.

35

Dextran 70-beta-alanine-DOTA-Dy is dissolved in saline solution and filled into 10 ml vials under aseptic

conditions. The solution contains 0.14 mmol Dy/ml.

Example 5

Intravenous paramagnetic MD agent (Dy(III)-DO3A)

Dysprosium(III) (1,4,7-triscarboxymethyl-1,4,7,10-tetra azacyclododecane (Dy(III)-DO3A) is prepared according to Example 10 in EP-A-232751.

An injectable solution is prepared which contains:

Dy(III)-DO3A	2 mmol
Water for injections	<u>ad</u> 20 ml

Dy(III)-DO3A is dissolved in water for injection, filled into 20 ml vials and sterilized by heating.

Example 6

Intravenous paramagnetic MD agent (Gd(III)-DTPA)

Gadolinium(III)-diethylenetriamine-N,N,N',N'',N'''-pentaacetic acid di-N-methylglucamine salt (Gd(III)-DTPA) was prepared according to Example 5 in US-A-4647447 (Schering).

An injectable solution is prepared which contains:

Gd(III)-DTPA dimeglumine	10 mmol
CaNa ₃ -DTPA	0.1 mmol
Water for injections	<u>ad</u> 20 ml

Gd(III)-DTPA dimeglumine and CaNa₃DTPA are dissolved in water for injections, filled into 20 ml vials and sterilized by heating.

Example 7Intravenous MD agent (Liposome formulation of Dy(III)-DTPA)

- 5 Dysprosium(III)-diethylenetriamine-N,N,N',N'',N'''-pentaacetic acid di-N-methylglucamine salt (Dy(III)-DTPA dimeglumine) is prepared according to Example 5 in US-A-4647447 (Schering).
- 10 Dy(III)-DTPA dimeglumine is encapsulated into small unilamellar vesicles according to the method described in EP-A-160552 (Vestar).

15 The purified liposome dispersion is filled into 50 ml vials and freeze dried. Each vial contains 0.5 mmol dysprosium.

The product is suspended in 20 ml saline before administration.

20

Example 8Intravenous paramagnetic MD agent for tumour studies (Monoclonal antibody labelled with dysprosium)

- 25 Diethylenetriamine-N,N,N',N'',N'''-pentaacetic acid is coupled to monoclonal antibodies according to the method described by D J Hnatowich et al. in Science 220: 613-615.

- 30 The antibody is as in Example 2.

1.0 mole equivalent dysprosium chloride is added during agitation, the pH-value is adjusted to 5.2 and the solution is agitated for 1 hour.

35

The solution is dialyzed against saline for 2 days then dialyzed against distilled water. The aqueous solution

is filled into 5 ml vials and lyophilized. Each vial contains 1 mmol dysprosium.

The product is dissolved in 5 ml or for lower concentrations 500 ml saline before use, in the latter case only 5 ml being injected.

Example 9

Oral superparamagnetic MD agent for abdominal studies

Particles of a sulphonated styrene-divinylbenzene copolymer matrix 3 micrometers in size and themselves carrying superparamagnetic particles to a total iron content of 19.4% by weight are prepared by the methods of WO-A-83/03920 (SINTEF)

A suspension for oral administration is prepared which contains:

Superparamagnetic particles	0.1g
Hydroxyethyl cellulose	8.0g
Methyl parahydroxybenzoate	0.7g
Propyl parahydroxybenzoate	0.15g
Ethanol	10.0g
Saccharin sodium	1.0g
Anis essence	0.2g
Water	<u>ad</u> 800g

Hydroxyethyl cellulose is dispersed in water with stirring for 2 hours. Saccharin sodium and a solution of anis essence, methyl and propyl parahydroxybenzoate in ethanol are slowly added. The superparamagnetic particles are dispersed in the solution under vigorous stirring.

The suspension is filled into a 800 ml bottle. The suspension contains 19.4 mg iron.

Example 10-11

Multi-channel SQUID analysis of 0.5% agar gels containing MD agents.

5

SQUID Instrument: Krenikon (SIMENS AG)

All samples were moved with the same frequency (appr. 4 Hz) during the experiments.

10

SQUID signals (16 channels) without sample is shown in Figure 1.

Example 10

15

MD agent: Superparamagnetic starch microspheres prepared according to (Schroder and Salford)

Concentration : 0.1 mmol/kg

20

Distance from detector : 1 cm

Results shown in Figure 2.

25

Example 11

MD agent: GdDTPA-BMA prepared according to US4687658 (Quay)

30

Concentration : 0.1 mmol/kg

Distance from detector : 1 cm

35 Results shown in Figure 3.

Example 12-13

Multi-channel SQUID analysis of the same samples as described in Example 10-11 after magnetization of the samples with a small, strong (about 0.3T) permanent magnet showed enhanced magnetometric effect compared to the non-magnetized samples.

(No corrections have been made for potential magnetization of the empty plastic test tubes).

Examples 14-15

SQUID analyses of the samples in Examples 19-26 are performed on an instrument detecting magnetic fields. Enhanced efficiency is observed.

(The instrument used in Examples 10-13 detects magnetic field gradients and not the absolute magnetic fields).

Examples 16 to 22Low concentration intravenous MD media

The MD media of Examples 1 to 7 are diluted, 1 part by volume with 99 parts by volume of water for injections to produce more dilute contrast media suitable for use with sensitive SQUID based magnetometers.

Still lower concentrations, e.g. at the 10^{-10} - 10^{-6} M level, can be produced by further dilution.

Claims

1. The use of a physiologically tolerable paramagnetic or superparamagnetic material for the manufacture of a diagnostic agent composition for use in magnetometric analysis of the human or non-human animal body.

2. Use as claimed in claim 1, wherein said paramagnetic material is porphyrin complex.

3. Use as claimed in claim 2, wherein said complex is a Mn(II) complex.

4. Use as claimed in any of claims 1 to 3, wherein said analysis comprises the generation of a magnetometric image of at least a part of the human or non-human animal body.

5. Use as claimed in claim 1, wherein said material is selected from paramagnetic lanthanide metal ion chelates, free superparamagnetic particles and matrix borne superparamagnetic particles.

6. Use as claimed in any of claims 1 to 5, for the manufacture of a said composition for use in magnetometric analysis performed using a superconducting quantum interference device (SQUID).

7. Use as claimed in any of claims 1 to 6, wherein said material contains a metal ion selected from Mn, Fe, Dy, Gd, Eu, Tb, Tm, Yb, Er and Ho ions.

8. Use as claimed in claim 7, wherein said metal ion is Dy(III).

9. A method of generating a magnetometric image of the human or non-human animal body comprising administering

to said body a physiologically tolerable paramagnetic or superparamagnetic material and generating a magnetometric signal of at least part of said body into which said material distributes.

10. A method as claimed in claim 9, wherein said signal is a magnetometric image of at least part of said body into which said material distributes.

11. A method as claimed in claim 10, wherein said image generated is a two or three dimensional structural image.

12. A method as claimed in any of claims 9 to 11, wherein said signal is generated using a superconducting quantum interference device (SQUID) magnetometer.

13. A method as claimed in claim 12, wherein said signal is generated using a multichannel SQUID system.

14. A method as claimed in any of claims 9 to 13, wherein a superparamagnetic material is used as a magnetometric diagnostic (MD) agent with no pre-magnetization thereof and no magnetic field or with a static magnetic field being imposed during signal generation.

15. A method as claimed in any of claims 9 to 13, wherein a paramagnetic material is used as a magnetometric diagnostic (MD) agent and at least part of said body is exposed to an imposed pulsed or invariant magnetic field during signal generation.

16. A method as claimed in any of claims 9 to 13, wherein said material contains a metal ion selected from Mn, Fe, Dy, Gd, Eu, Tb, Tm, Yb, Er and Ho ions.

17. A method as claimed in claim 16, wherein said metal ion is Dy(III).

18. A process for detecting variations in magnetic susceptibility within a human or non-human animal body, comprising administering to said body a physiologically tolerable paramagnetic or superparamagnetic material, and with a magnetometer continuously or repeatedly monitoring the magnetic susceptibility of at least a part of said body into which said material distributes.

19. A process as claimed in claim 18 comprising generating a magnetometric image.

20. A process as claimed in either of claims 18 and 19, wherein said magnetometer is a superconducting quantum interference device (SQUID) magnetometer.

21. A process as claimed in claim 20, wherein said magnetometer is a multichannel SQUID system.

22. A process as claimed in any of claims 18 to 22, wherein a superparamagnetic material is used as a magnetometric diagnostic (MD) agent with no pre-magnetization thereof and no magnetic field or with a static magnetic field being imposed during signal generation.

23. A process as claimed in any of claim 18 to 22, wherein a paramagnetic material is used as a magnetometric diagnostic (MD) agent and at least part of said body is exposed to an imposed pulsed or invariant magnetic field during signal generation.

24. A process as claimed in any of claim 18 to 22, wherein material contains a metal ion selected from Mn,

Fe, Dy, Gd, Eu, Tb, Tm, Yb, Er and Ho ions.

25. A process as claimed in claim 24, wherein said metal ion is Dy(III).

26. The use of a physiologically tolerable paramagnetic or superparamagnetic material for the manufacture of a diagnostic composition for use in a process as claimed in any of claims 18 to 25.

27. A magnetic susceptibility magnetometric diagnostic medium in aqueous form containing a physiologically tolerable paramagnetic or superparamagnetic material together with at least one pharmaceutical carrier or excipient, the magnetic susceptibility of said medium being from 10^{-12} to 10^{-6} emu/g at STP.

28. A medium as claimed in claim 24, with a magnetic susceptibility of from 10^{-9} to 10^{-8} emu/g at STP.

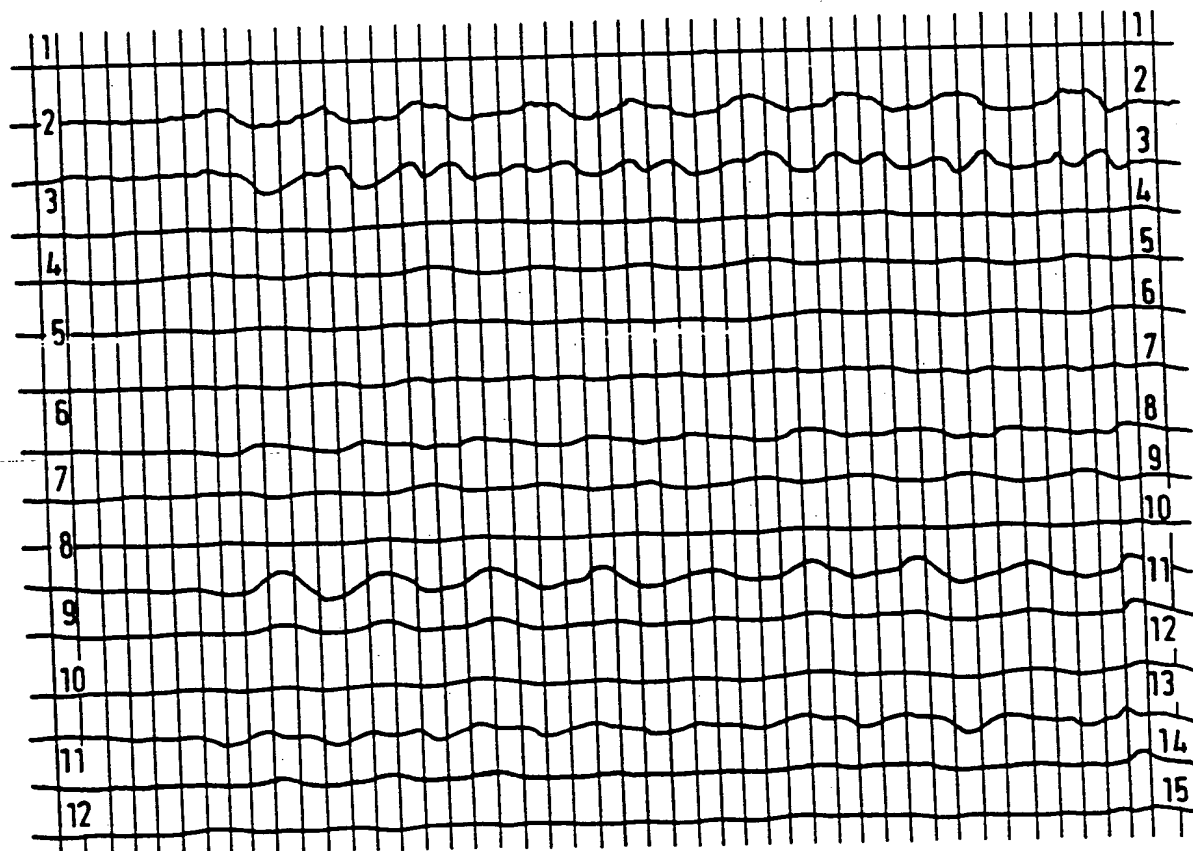
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FIG. 1

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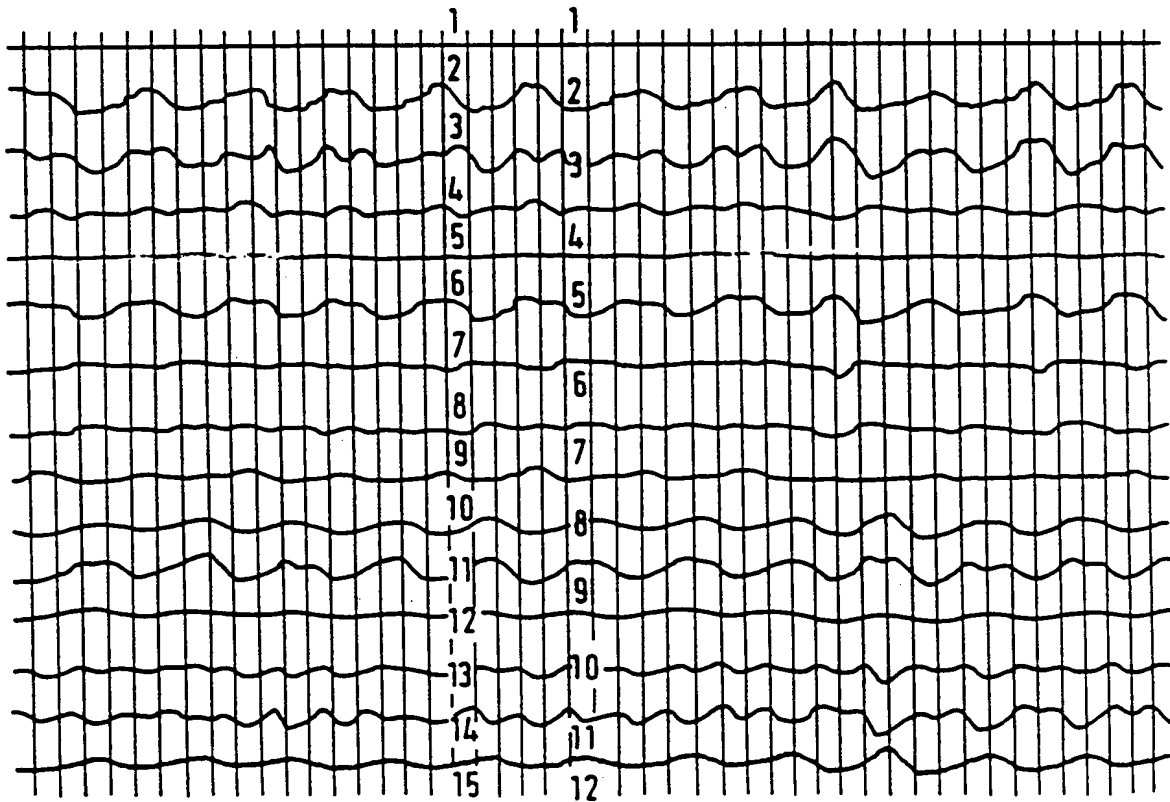
2/3

FIG. 2



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FIG. 3



INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 91/00619

I. CLASSIFICATION F SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁵: A 61 K 49/00

II. FIELDS SEARCHED

Minimum Documentation Searched ⁷

Classification System

Classification Symbols

IPC⁵

A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched ⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	IEEE Transactions on Magnetics, volume MAG-11 no. 2, March 1975, (New York, US) D. Cohen: "Measurements of the magnetic fields produced by the human heart, brain and lungs", pages 694-700, see page 694, abstract	1,4-7,27
Y	cited in the application --	1-8,27
X	IEEE Transactions on Magnetics, volume MAG-16, no. 5, September 1980 (New York, US) D.E. Farrell et al.: "Magnetic measurement of human iron stores", pages 818-823, see page 818, abstract; page 819, paragraph 7 - page 820, paragraph 1	1,4-7,27
Y	cited in the application --	1-8,27
X	WO, A, 85/02772 (SCHRÖDER) 4 July 1985 see page 2, line 21 - page 3, line 1; page 5, line 35 - page 6, line 32	1,4-7,27
Y	cited in the application ./.	1-8,27

* Special categories of cited documents: ¹⁰

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

8th July 1991

Date of Mailing of this International Search Report

13.09.91

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Natalie Weinberg

FURT

III. DOCUMENTS CONSIDERED TO BE RELEVANT (Continued from Form PCT/ISA/206 Annex)		
Category*	Citation of Document with indication, where appropriate, of the relevant passages	Relevant to Claim N°
Y	WO, A, 88/00060 (ADVANCED MAGNETICS INC.) 14 January 1988, see page 10, line 29 - page 17, line 9 cited in the application --	1,4-7,27
Y	WO, A, 86/06605 (THE GENERAL HOSPITAL CORP.) 20 November 1986, see page 1, line 13 - page 3, line 3; page 9, lines 22-31 cited in the application --	1-8,27
Y	Chemical Abstracts, volume 104, no. 24, 16 June 1986, (Columbus, Ohio, US) M.L. Cofield et al.: "Low-temperature magnetic susceptibility and zero-field splitting in some high-spin manganese (III) compounds", see page 704, abstract 217805s, & Inorg. Chim. Acta 1986, 112(1), 1-4 --	1-7,27
P,X	WO, A, 90/07322 (GORDON) 12 July 1990 see claims 17-19, 24 -----	1-8,27

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers ~~xxx~~ because they relate to subject matter not required to be searched by this Authority, namely:
~~xx~~ Claims 9-26, 28

Please see attached sheet ./. .

2. ☒ Claim numbers ~~xxx~~ because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-8, 27 searched incompletely
Also see attached sheet ./. .

3. ☐ Claim numbers..... because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9100619

SA 46226

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 30/08/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8502772	04-07-85	SE-B- 463651	07-01-91
		DE-A- 3475269	29-12-88
		EP-A, B 0166755	08-01-86
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		EP-A- 0275285	27-07-88
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		US-A- 4951675	28-08-90
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		CA-A- 1264663	23-01-90
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